

Amendments to the Specification:

Replace the paragraph beginning on page 4, line 22,  
with the following amended paragraph:

Several embodiments are provided by the invention.  
The first embodiment, to be referred to herein as the "G-CSF-inducing embodiment" involves the use of an active ingredient, which may be an A<sub>3</sub>Rag-A<sub>3</sub>RAg or an A<sub>1</sub>Rag-A<sub>1</sub>RAg to yield secretion of the G-CSF within the body of a treated subject. G-CSF is known to stimulate proliferation and differentiation of hematopoietic progenitors and controls the functional activities of neutrophils and macrophages. Thus, a G-CSF-inducing agent such as those mentioned above, may have a high therapeutic value, for example, in countering (i.e. preventing, reducing or ameliorating) myelotoxicity.

Replace the paragraph beginning on page 10, line 10,  
with the following amended paragraph:

By one embodiment, the active ingredient according to the invention is a nucleoside derivative. By the term "nucleoside" it is meant any compound comprising a sugar, preferably ribose or deoxyribose, or a purine or pyrimidine base or a combination of a sugar with a purine or pyrimidine base preferably by way of N-glycosyl link. The term "nucleoside derivative" will be used to denote herein a naturally occurring nucleoside as defined hereinabove, a

synthetic nucleoside or a nucleoside which underwent chemical modifications by way of insertion/s, deletion/s or exocyclic and endocyclic substitution/s of group/s therein or conformational modifications which provide a derivative with the desired biological effect.

Replace the paragraph beginning on page 11, line 6, with the following amended paragraph:

Y is an oxygen- or sulfur atom or CH<sub>2</sub>ef carbon atoms;

Replace the paragraph beginning on page 12, line 8, with the following amended paragraph:

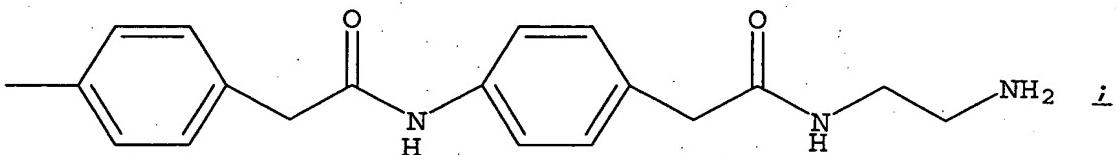
- R<sub>2</sub> is selected from the group consisting of hydrogen, halo, C<sub>1</sub>-C<sub>10</sub> alkylether, amino, hydrazido, C<sub>1</sub>-C<sub>10</sub> alkylamino, C<sub>1</sub>-C<sub>10</sub> alkoxy, C<sub>1</sub>-C<sub>10</sub> thioalkoxy, pyridylthio, C<sub>2</sub>-C<sub>10</sub> alkenyl, + C<sub>2</sub>-C<sub>10</sub> alkynyl, thio, and C<sub>1</sub>-C<sub>10</sub> alkylthio; and

Replace the paragraphs beginning on page 12, lines 12 and 15, and page 13, lines 1 and 3, with the following amended paragraph:

- R<sub>3</sub> is an -NR<sub>4</sub>R<sub>5</sub> group, with R<sub>4</sub> being hydrogen, or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with Z being O, S, or NR<sup>a</sup> with R<sup>a</sup> having the above meanings, and, when

and R<sub>5</sub>, where R<sub>4</sub> is hydrogen, is R<sub>5</sub> being selected from the group consisting of R- and S-1-phenylethyl, benzyl, phenylethyl or anilide groups, each such group being

unsubstituted or substituted in one or more positions with a substituent selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, amino, halo, C<sub>1</sub>-C<sub>10</sub> haloalkyl, nitro, hydroxyl, acetamide acetamido, C<sub>1</sub>-C<sub>10</sub> alkoxy, and sulfonic acid or a salt thereof; or R<sub>4</sub> is R<sub>5</sub> being benzodioxanemethyl, fururyl, L-propylalanylaminobenzyl,  $\beta$ -alanylamine, benzylalanylaminebenzyl, T-BOC- $\beta$ -alanylamine, benzylalanylaminobenzyl, phenylamino, carbamoyl, phenoxy or C<sub>1</sub>-C<sub>10</sub> cycloalkyl; or R<sub>5</sub> is being a group of the following formula:

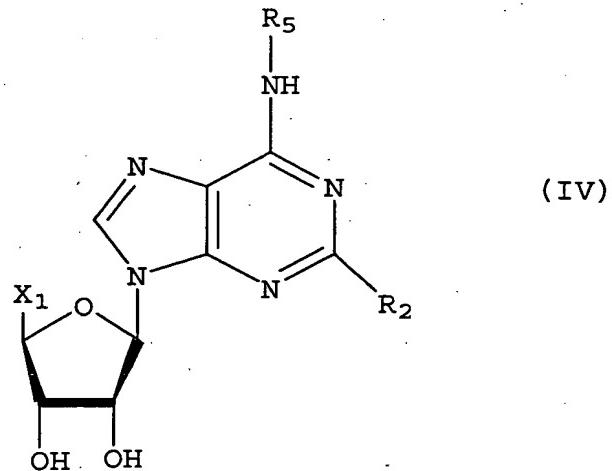
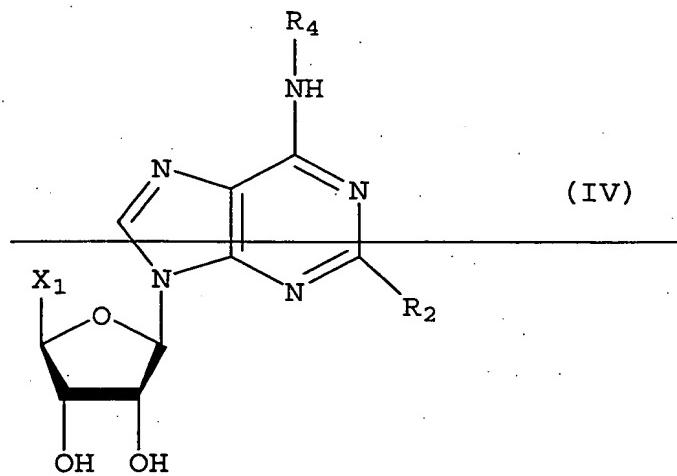


or, when R<sub>4</sub> is, a group selected from alkyl, substituted alkyl, or aryl-NH-C(Z)-, then, R<sub>5</sub> is being selected from the group consisting of substituted or unsubstituted heteroaryl-NR<sup>a</sup>-C(Z)-, heteroaryl-C(Z)-, alkaryl-NR<sup>a</sup>-C(Z)-, alkaryl-C(Z)-, aryl-NR-C(Z)- and aryl-C(Z)-, wherein with Z having the above defined meanings;

Following the paragraph on page 13 that ends on line 8, insert the following new paragraph:

or a suitable salt of the compound defined above,  
e.g. a triethylammonium salt thereof.

Replace the formula at page 13, line 11, with the following corrected formula:



Replace the paragraph beginning on page 13, line 12, with the following amended paragraph:

wherein X<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub>-R<sub>5</sub> are as defined above and

Replace the paragraph beginning on page 13, line 13, with the following amended paragraph:

Preferred active ingredients according to this embodiment of the invention may generally be referred to as N<sup>6</sup>N<sup>6</sup>-benzyladenosine-5'-uronamides and derivatives thereof found to be A3-selective adenosine receptor agonists.

Examples for such derivatives are N<sup>6</sup>-2-(4-aminophenyl)ethyladenosine (APNEA), N<sup>6</sup>-(4-amino-3-iodobenzyl)adenosine-5'-(N-methyluronamide) (AB-MECA) and 1-deoxy-1-{6-[({3-iodophenyl}methyl)amino]-9H-purine-9-yl}-N-methyl-β-D-ribofuranuron amide ~~ribofuranuronamide~~, the latter also referred to in the art as N<sup>6</sup>-3-iodobenzyl iodobenzyl-5'-methylcarboxamido ~~adenosine~~, N<sup>6</sup>N<sup>6</sup>-(3-iodobenzyl iodobenzyl)adenosine-5'-N-methyl-uronamide ~~methyluronimide~~ and herein above and below by the abbreviation IB-MECA or a chlorinated derivative of IB-MECA ( $R_2=Cl$ ), referred to herein as Cl-IB-MECA, IB-MECA and Cl-IB-MECA being currently particularly preferred.

Replace the paragraph beginning on page 14, line 4, with the following amended paragraph:

According to another embodiment of the invention, the active ingredient may be an adenosine derivative generally referred to as N<sup>6</sup>-benzyl adenosine-5'-alkyluronamide-N<sup>1</sup>-oxide N<sup>6</sup>-benzyladenosine-5'-N-alkyluronamide-N<sup>1</sup>-oxide or N<sup>6</sup>-benzyladenosine-5'-N-dialyluren amide-N<sup>1</sup>-oxide N<sup>6</sup>-benzyladenosine-5'-N-dialyluronamide-N<sup>1</sup>-oxide.

Replace the paragraph beginning on page 14, line 20,  
with the following amended paragraph:

R<sub>7</sub> and R<sub>8</sub> may be the same or different and are selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> cycloalkyl, R- or S-1-phenylethyl, an unsubstituted benzyl or anilide group, and a phenyletherphenylethyl ~~or~~ benzyl group substituted in one or more positions with a substituent selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, amino, halo, C<sub>1</sub>-C<sub>10</sub> haloalkyl, nitro, hydroxyl, ~~acetamido~~acetamido, C<sub>1</sub>-C<sub>10</sub> alkoxy, and sulfonic acid;

Replace the paragraph beginning on page 15,  
line 5, with the following amended paragraph:

- R<sub>9</sub> is selected from the group consisting of halo, benzyl, phenyl, C<sub>3</sub>-C<sub>10</sub> ~~eyelalkylcycloalkyl~~, and C<sub>1</sub>-C<sub>10</sub> alkoxy; or a salt of such a compound, for example, a triethylammonium salt thereof.

Following the paragraph on page 15 that ends on line 10, insert the following new paragraphs:

More specifically, the following specific examples are specified in US 5,688,774 at column 4, line 67; column 5, line 16; column 5, lines 39-45; column 6, lines 21-42; column 7, lines 1-11; column 7, lines 34-36; and column 7, lines 60-61:

N<sup>6</sup>-(3-iodobenzyl)-9-methyladenine;

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N<sup>6</sup>- (3-iodobenzyl) -9-hydroxyethyladenine;  
R-N<sup>6</sup>- (3-iodobenzyl) -9- (2,3-dihydroxypropyl) adenine;  
S-N<sup>6</sup>- (3-iodobenzyl) -9- (2,3-dihydroxypropyl) adenine;  
N<sup>6</sup>- (3-iodobenzyladenin-9-yl) acetic acid;  
N<sup>6</sup>- (3-iodobenzyl) -9- (3-cyanopropyl) adenine;  
2-chloro-N<sup>6</sup>- (3-iodobenzyl) -9-methyladenine;  
2-amino-N<sup>6</sup>- (3-iodobenzyl) -9-methyladenine;  
2-hydrazido-N<sup>6</sup>- (3-iodobenzyl) -9-methyladenine;  
N<sup>6</sup>- (3-iodobenzyl) -2-methylamino-9-methyladenine;  
2-dimethylamino-N<sup>6</sup>- (3-iodobenzyl) -9-methyladenine;  
N<sup>6</sup>- (3-iodobenzyl) -9-methyl-2-propylaminoadenine;  
2-hexylamino-N<sup>6</sup>- (3-iodobenzyl) -9-methyladenine;  
N<sup>6</sup>- (3-iodobenzyl) -2-methoxy-9-methyladenine;  
N<sup>6</sup>- (3-iodobenzyl) -9-methyl-2-methylthioadenine;  
N<sup>6</sup>- (3-iodobenzyl) -9-methyl-2-(4-pyridylthio) adenine;  
(1S,2R,3S,4R)-4-(6-amino-2-phenylethylamino-9H-purin-9-yl)cyclopentane-1,2,3-triol;  
(1S,2R,3S,4R)-4-(6-amino-2-chloro-9H-purin-9-yl)cyclopentane-1,2,3-triol;  
(±)-9-[2α,3α-dihydroxy-4β-(N-methylcarbamoyl)cyclopent-1β-yl)]-N<sup>6</sup>- (3-iodobenzyl) -adenine;  
2-chloro-9-(2'-amino-2',3'-dideoxy-β-D-5'-methylarabino-furonamido)-N<sup>6</sup>- (3-iodobenzyl) adenine;

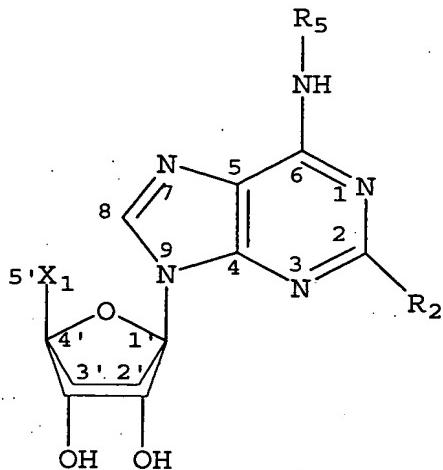
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2-chloro-9-(2',3'-dideoxy-2'-fluoro- $\beta$ -D-5'-methyl-arabino-furonamido)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
9-(2-acetyl-3-deoxy- $\beta$ -D-5-methyl-ribofuronamido)-2-chloro-N<sup>6</sup>(3-iodobenzyl)adenine;  
2-chloro-9-(3-deoxy-2-methanesulfonyl- $\beta$ -D-5-methyl-ribofuronamido)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
2-chloro-9-(3-deoxy- $\beta$ -D-5-methyl-ribofuronamido)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
2-chloro-9-(3,5-1,1,3,3-tetraisopropyldisiloxy- $\beta$ -D-5-ribofuranosyl)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
2-chloro-9-(2',3'-O-thiocarbonyl- $\beta$ -D-5-methyl-ribofuronamido)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
9-(2-phenoxythiocarbonyl-3-deoxy- $\beta$ -D-5-methyl-ribofuronamido)-2-chloro-N<sup>6</sup>-(3-iodobenzyl)adenine;  
1-(6-benzylamino-9H-purin-9-yl)-1-deoxy-N,4-dimethyl- $\beta$ -D-ribofuranosiduronamide;  
2-chloro-9-(2,3-dideoxy- $\beta$ -D-5-methyl-ribofuronamido)-N<sup>6</sup>-benzyladenine;  
2-chloro-9-(2'-azido-2',3'-dideoxy- $\beta$ -D-5'-methyl-arabino-furonamido)-N<sup>6</sup>-benzyladenine;  
2-chloro-9-( $\beta$ -D-erythrocyclonoside)-N<sup>6</sup>-(3-iodobenzyl)adenine;  
N<sup>6</sup>-(benzodioxanemethyl)adenosine;

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1- (6-furfurylamino-9H-purin-9-yl)-1-deoxy-N-methyl-  
 $\beta$ -D-ribofuranosiduronamide;  
N<sup>6</sup>- [3- (L-prolylamino)benzyl]adenosine-5'-N-  
methyluronamide;  
N<sup>6</sup>- [3- ( $\beta$ -alanylamino)benzyl]adenosine-5'-N-  
methyluronamide;  
N<sup>6</sup>- [3- (N-T-Boc- $\beta$ -alanylamino)benzyl]adenosine-5'-N-  
methyluronamide  
6- (N'-phenylhydrazinyl)purine-9- $\beta$ -ribofuranoside-5'-  
N-methyluronamide;  
6- (O-phenylhydroxylamino)purine-9- $\beta$ -ribofuranoside-  
5'-N-methyluronamide;  
9- ( $\beta$ -D-2',3'-dideoxyerythrofuranosyl)-N<sup>6</sup>- [(3- $\beta$ -  
alanylamino)benzyl]adenosine;  
9- ( $\beta$ -D-erythrofuranoside)-2-methylamino-N<sup>6</sup>- (3-  
iodobenzyl)adenine;  
2-chloro-N- (3-iodobenzyl)-9- (2-tetrahydrofuryl)-9H-  
purin-6-amine;  
2-chloro- (2'-deoxy-6'-thio-L-arabinosyl)adenine; and  
2-chloro- (6'-thio-L-arabinosyl)adenine.

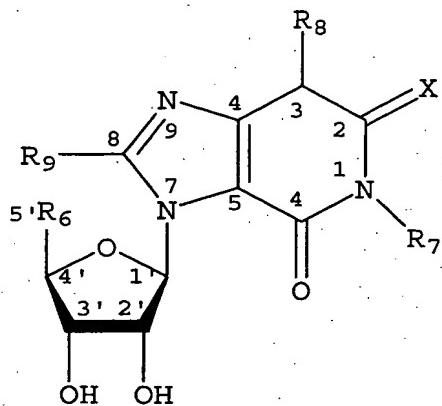
In US 5,773,423 at column 6, line 39, to column 7,  
line 14, preferred compounds include those of the formula:



wherein  $X_1$  is  $R^aR^bNC(=O)$ , wherein  $R^a$  and  $R^b$  may be the same or different and are selected from the group consisting of hydrogen,  $C_1-C_{10}$  alkyl, amino,  $C_1-C_{10}$  haloalkyl,  $C_1-C_{10}$  aminoalkyl, and  $C_3-C_{10}$  cycloalkyl,  $R_2$  is selected from the group consisting of hydrogen, halo,  $C_1-C_{10}$  alkoxy, amino,  $C_2-C_{10}$  alkenyl, and  $C_2-C_{10}$  alkynyl, and  $R_5$  is selected from the group consisting of  $R$ - and S-1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of  $C_1-C_{10}$  alkyl, amino, halo,  $C_1-C_{10}$  haloalkyl, nitro, hydroxy, acetamido,  $C_1-C_{10}$  alkoxy, and sulfo. More preferred compounds include those of the above formula wherein  $R^a$  and  $R^b$  may be the same or different and are selected from the group consisting of hydrogen and  $C_1-C_{10}$  alkyl, particularly when  $R_2$  is hydrogen or halo, especially hydrogen. Additional preferred compounds are those compounds wherein  $R^a$  is hydrogen and  $R_2$  is hydrogen,

particularly when R<sub>5</sub> is unsubstituted benzyl. More preferred compounds are such compounds wherein R<sup>b</sup> is a C<sub>1</sub>-C<sub>10</sub> alkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl, particularly a C<sub>1</sub>-C<sub>10</sub> alkyl, and more particularly methyl. Especially preferred are those compounds where R<sup>a</sup> is hydrogen, R<sup>b</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl, and R<sub>5</sub> is R- or S-1-phenylethyl or a benzyl substituted in one or more positions with a substituent selected from the group consisting of halo, amino, acetamido, C<sub>1</sub>-C<sub>10</sub> haloalkyl, and sulfo, where the sulfo derivative is a salt, such as a triethylammonium salt. An example of an especially preferred compound is IB-MECA. In addition, those compounds in which R<sub>2</sub> is a C<sub>2</sub>-C<sub>10</sub> alkyne of the formula R<sup>d</sup>-C=C- where R<sup>d</sup> is a C<sub>1</sub>-C<sub>8</sub> alkyl are particularly preferred. Also preferred are those compounds wherein R<sub>2</sub> is other than hydrogen, particularly those wherein R<sub>2</sub> is halo, C<sub>1</sub>-C<sub>10</sub> alkylamino, or C<sub>1</sub>-C<sub>10</sub> alkylthio, and, more preferably, when additionally R<sup>a</sup> is hydrogen, R<sup>b</sup> is a C<sub>1</sub>-C<sub>10</sub> alkyl, and/or R<sub>5</sub> is a substituted benzyl. Such preferred compounds include 2-chloro-N<sup>6</sup>-(3-iodobenzyl)-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine, N<sup>6</sup>-(3-iodobenzyl)-2-methylamino-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine, and N<sup>6</sup>-(3-iodobenzyl)-2-methylthio-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine.

Additional preferred compounds are specified in US 5,773,423 at column 7, line 60, through column 8, line 6, as modified xanthine-7-ribosides having the formula:



Particularly preferred are those compounds wherein X is O, R<sub>6</sub> is R<sup>a</sup>R<sup>b</sup>NC(=O), wherein R<sup>a</sup> and R<sup>b</sup> may be the same or different and are selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, amino, C<sub>1</sub>-C<sub>10</sub> haloalkyl, C<sub>1</sub>-C<sub>10</sub> aminoalkyl, and C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sub>7</sub> and R<sub>8</sub> may be the same or different and are selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, R- and S-1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C<sub>1</sub>-C<sub>10</sub> alkyl, amino, halo, C<sub>1</sub>-C<sub>10</sub> haloalkyl, nitro, hydroxy, acetamido, C<sub>1</sub>-C<sub>10</sub> alkoxy, and sulfo, and R<sub>9</sub> is selected from the group consisting of halo, benzyl, phenyl, and C<sub>3</sub>-C<sub>10</sub> cycloalkyl.

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WO 99/06053 discloses in examples 19-33 and originally filed claim 13, compounds selected from the group consisting of:

$N^6$ - (4-biphenyl-carbonylamino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (2,4-dichlorobenzyl-carbonylamino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (4-methoxyphenyl-carbonylamino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (4-chlorophenyl-carbonylamino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (phenyl-carbonylamino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (benzylcarbamoyl-amino)-adenosine-5'-N-ethyluronamide;

$N^6$ - (4-sulfonamido-phenylcarbamoyl)-adenosine-5'-N-ethyluronamide;

$N^6$ - (4-acetyl-phenylcarbamoyl)-adenosine-5'-N-ethyluronamide;

$N^6$ - ((R)- $\alpha$ -phenylethylcarbamoyl)-adenosine-5'-N-ethyluronamide;

$N^6$ - ((S)- $\alpha$ -phenylethylcarbamoyl)-adenosine-5'-N-ethyluronamide;

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N<sup>6</sup>- (5-methyl-isoxazol-3-yl-carbamoyl)-adenosine-5'-N-ethyluronamide;

N<sup>6</sup>- (1,3,4-thiadiazol-2-yl-carbamoyl)-adenosine-5'-N-ethyluronamide;

N<sup>6</sup>- (4-n-propoxy-phenylcarbamoyl)-adenosine-5'-N-ethyluronamide;

N<sup>6</sup>-bis- (4-nitrophenylcarbamoyl)-adenosine-5'-N-ethyluronamide; and

N<sup>6</sup>-bis- (5-chloro-pyridin-2-yl-carbamoyl)-adenosine-5'-N-ethyluronamide.

Replace the paragraph beginning on page 17, line 10,  
with the following amended paragraph:

- R<sub>2</sub> represents a hydrogen; halogen; substituted or unsubstituted lower alkyl or alkenyl group; lower haloalkyl or haloalkenyl; cyano; acetamide~~acetamido~~; lower alkoxy; lower alkylamino; NR<sup>d</sup>R<sup>e</sup> where R<sup>d</sup> and R<sup>e</sup> are independently hydrogen, lower alkyl, phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or haloalkyl such as trifluoromethyl or alkoxy; or -SR<sup>f</sup> where R<sup>f</sup> is hydrogen, lower alkyl, lower alkanoyl, benzoyl or phenyl;

Replace the paragraph beginning on page 21, line 6,  
with the following amended paragraph:

Pharmaceutically acceptable salts of the above active ingredients include those derived from pharmaceutically

acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphoric, nitric, perchloric, fumaric, maleic, phosphoric, glycolicglycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids.

Replace the paragraph beginning on page 22, line 1, with the following amended paragraph:

The pharmaceutical composition of the invention may comprise the active ingredient as such, but may be combined with other ingredients which may be a pharmaceutically acceptable carrier, diluent, excipient, additive and/or adjuvant, as known to the artisan, e.g., for the purposes of adding flavors, colors, lubrication or the like to the pharmaceutical composition. Evidently, the pharmaceutically acceptable carrier/s, diluent/s, excipient/s, additive/s employed according to the invention generally refer to inert, non-toxic solid or liquid fillers, diluents or encapsulating materials which preferably do not react with the compounds within the composition of the invention.

Replace the paragraph beginning on page 29, line 2, with the following amended paragraph:

**Fig. 13 shows the effect of anti-G-CSF antibodies on the number of white blood cells (WBC) in control mice, mice**

treated with a ~~chemotheapeutie~~chemotherapeutic drug and mice treated with a chemotherapeutic drug and with Cl-IB-MECA, administered orally (6 µg/kg body weight, in 0.2 ml PBS). The number of WBC following injection of anti-G-CSF antibodies is represented by the light-colored columns. All results are presented as percent of control (control = 100%).

Replace the paragraph beginning on page 29, line 12, with the following amended paragraph:

Fig. 15 shows results of experiments similar to that of Fig. 14, where the size of the tumor developed in nude mice following injection of HCT-116 human colon carcinoma cells was measured. Four groups were tested: a control group, a group receiving the chemotherapeutic drug 5-FU, a group administered orally with Cl-IB-MECA and a group receiving a combined ~~treatment~~treatment of 5-FU and Cl-IB-MECA.

Replace the paragraph beginning on page 31, line 19, with the following amended paragraph:

Female ICR, C57BL/6J or mice (BALB/C origin) mice aged 3 months, weighing an average of 25 g were used. The mice were purchased from Harlan Laboratories, Jerusalem, ISRAEL. Standardized pelleted diet and tap water were supplied.

Replace the paragraph beginning on page 35, line 9, with the following amended paragraph:

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2. Chemotherapy group: one i.p. injection of cyclophosphamide 24 hours after inoculation of tumor cells and daily i.p. injection of 1 ml saline per mouse from day of tumor inoculation until the mice were sacrificed.

Replace the paragraph beginning on page 35, line 16, with the following amended paragraph:

4. A3RAG + chemotherapy group: one i.p. injection of cyclophosphamide 24 hours after inoculation of tumor cells and daily oral administration of 3  $\mu$ g/kg body weight of IB-MECA.

Replace the paragraph beginning on page 35, line 23, with the following amended paragraph:

A further experiment was conducted in order to evaluate the chemoprotective effect of A3RAG. Mice were treated with cyclophosphamide (50 mg/kg body weight in 0.3 ml PBS). After 48 and 72 hours from administration of the cytotoxic drug, the mice were injected i.p. with adenosine (25  $\mu$ g/kg body weight) or with IB-MECA (3 or 6  $\mu$ g/kg body weight in 0.2 ml PBS). The number of white blood cells (WBC) and neutrophils was tested. The results are shown in Figs. 10A (WBCs) and 10B (neutrophils), respectively.

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Replace the paragraph beginning on page 36, line 1,  
with the following amended paragraph:

As can be seen, mice treated with cyclophosphamide only exhibited a decline in the number of peripheral blood leukocytes and neutrophils as compared to the group treated only with IB-MECA. When adenosine or IB-MECA were administered, the total white blood cell count was restored with the latter having a very pronounced effect, yielding a complete recovery after 168 hours (7 days).

Replace the paragraph beginning on page 37, line 4,  
with the following amended paragraph:

ICR mice were treated with doxorubicin (injection of 10 mg/kg i.p. in 0.5 ml PBS). After 24, 48 and 72 hours from administration of the cytotoxic drug, the mice were orally administered with Cl-IB-MECA (6 µg/kg body weight). At 72 hours, 96 hours, 120 hours and 144 hours, the mice were sacrificed and blood samples were withdrawn. In addition, bone marrow cells were aspirated from the femur of the mice and a cell count of nucleated cells from this aspirated preparation was made, following staining of the preparation with Coomassie Blue.

Replace the paragraph beginning on page 37, line 18,  
with the following amended paragraph:

The results of the white blood cell count can be seen in Fig. 12A, and that of the bone marrow nucleated cell count in Fig. 12B. These results clearly show that upon administration of Cl-IB-MECA, there is a marked increase in the number of peripheral white blood cells as well as in the number of bone marrow nucleated cells. This is evident to the protecting effect of the A3RAg against myleotoxic myelotoxic effects of doxorubicin.

Replace the paragraph beginning on page 37, line 31, with the following amended paragraph:

Group 3: Chemotherapy - administration of cyclophosphamide CYP - 50 mg/kg body weight).

Replace the paragraph beginning on page 38, line 12, with the following amended paragraph:

Cl-IB-MECA was given orally (in 0.2 ml PBS) at 48 hours and 72 hours following the administration of the cyclophosphamide.

Replace the paragraph beginning on page 38, line 20, with the following amended paragraph:

The results of the WBC count is shown in Fig. 13. As can be seen, mice treated with cyclophosphamide only showed a decline in the number of peripheral blood WBC. In the group that was treated

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with Cl-IB-MECA, the WBC counts and the percentage of neutrophils were significantly higher in comparison to the chemotheapeutic treated group (results regarding transfer of neutrophils not shown). When anti-G-CSF antibodies were administered to the control or the chemotherapy groups, an expected decline in the number of WBC was observed. Administration of anti-G-CSF antibodies to the mice treated with the combination of the chemotherapeutic drug and Cl-IB-MECA, cancelled the protective effect of Cl-IB-MECA, as can clearly be seen in Fig. 13. These results lead to the conclusion that the protective effect of Cl-IB-MECA on the myeloid system is mediated through the ability of a Cl-IB-MECA to promote the production and secretion of G-CSF.

Replace the heading beginning on page 39, line 4, with the following amended heading:

**Example 8: Cl-IB-MECA inhibits the development of HCT-116 human colon carcinoma in nude mice**

Replace the paragraph beginning on page 40, line 5, with the following amended paragraph:

Bone marrow cells ( $3 \times 10^6$  cell/ml) were incubated in wells of 96 microtiter plates. Cl-IB-MECA at a final concentration of 10 nM was added with or without anti-G-CSF antibodies, at a final concentration of 0.05 and 0.5  $\mu$ g/ml. Cell proliferation was measured by [<sup>3</sup>H]-thymidine incorporation assay. The results are shown in Fig. 17.

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Replace the paragraph beginning on page 41, line 2,  
with the following amended paragraph:

An example similar to that of Example 4, was  
~~performed~~performed with Cl-IB-MECA and the results are shown in  
Figs. 19A and 19B demonstrating the chemoprotective activity  
of Cl-IB-MECA.